CELLULAR AND MOLECULAR IMMUNOLOGY

ABUL K. ABBAS, M.B.B.S.
Professor of Pathology
Harvard Medical School and Brigham and Women's Hospital
Boston, Massachusetts

ANDREW H. LICHTMAN, M.D., Ph.D.
Assistant Professor of Pathology
Harvard Medical School and Brigham and Women's Hospital
Boston, Massachusetts

JORDAN S. POBER, M.D., Ph.D.
Professor of Pathology and Immunobiology
Yale University School of Medicine
New Haven, Connecticut

W.B. SAUNDERS COMPANY
Harcourt Brace Jovanovich, Inc.
Philadelphia London Toronto Montreal Sydney Tokyo

W. B. Saunders Company
Harcourt Brace Jovanovich, Inc.
The Curtis Center
Independence Square West
Philadelphia, PA 19106

Library of Congress Cataloging-in-Publication Data

Abbas, Abul K.
Cellular and molecular immunology / Abul K. Abbas, Andrew H. Lichtman, Jordan S. Pober.
p. cm.
ISBN 0-7216-3032-4
1. Cellular immunity. 2. Immunity—Molecular aspects. I. Lichtman, Andrew H. II. Pober, Jordan S. III. Title.
[DNLM: 1. Immunity, Cellular. 2. Lymphocytes—immunology. QW 568 A122c]
QR185.5.A23 1991
616.07'9—dc20
DNLM/DLC

Editor: Martin J. Wonsiewicz
Designer: Paul M. Fry
Production Manager: Peter Faber
Manuscript Editor: Carol Robins
Illustrator: Risa Clow
Illustration Coordinator: Brett MacNaughton
Indexer: Linda Van Pelt

Cellular and Molecular Immunology

ISBN 0-7216-3032-4

Printed in the United States of America.

Last digit is the print number: 9 8 7 6 5 4 3

ally related, or homologous, to each other and, to a lesser extent, to V_κ and V_λ.

HEAVY CHAIN STRUCTURE

All heavy chain polypeptides, regardless of antibody isotype, contain a tandem series of approximately 110 amino acid residue sequences. These sequences are homologous to each other, and all undergo characteristic folding into 12 kD Ig domains. As in light chains, the amino terminal variable, or V_H, domain displays the greatest sequence variation among heavy chains and the most variable residues are concentrated into three short (up to ten amino acid residue) stretches called CDR1, CDR2, and CDR3 (Fig. 3-4). Also similar to light chains, the heavy chain CDR3 shows greater sequence variability than CDR1 or CDR2.

The remainder of the heavy chain, which forms the constant (C) region, differs among isotypes; however, it is invariant among the member antibodies within a particular isotype. In IgM and IgE antibodies, the constant region is of sufficient length to form four separate Ig domains. In IgG, IgA, and IgD antibodies, the shorter constant regions form three Ig domains. (In the mouse, the δ chain gene has undergone a deletion such that the protein product forms only two Ig domains.)

In γ, α, and δ heavy chains, there is a nonglobular region of amino acid sequence, containing from about ten (in $\alpha 1$, $\alpha 2$, $\gamma 1$, $\gamma 2$, and $\gamma 4$) to over 60 (in $\gamma 3$ or δ) residues, located between the first and second constant region domains (called C_H1 and C_H2, respectively). Although portions of this sequence form rodlike helical structures, other portions assume a random and flexible conformation, permitting molecular motion between C_H1 and C_H2. For this reason, this portion of the heavy chain is called the **hinge.** Some of the greatest differences between the constant regions of the IgG subclasses are concentrated in the hinge region. For steric reasons, antibody subtypes with flexible hinges may be better able to use more than one antigen-binding site to attach to a particular antigen; as discussed later in this chapter, binding involving more than one attachment point will increase the strength of attachment.

All heavy chains may be expressed in one of two molecular forms that differ in amino acid sequence on the carboxy terminal side of the last C_H domain. The secretory form, found in blood plasma, terminates with a sequence containing charged and hydrophilic amino acids. The membrane form, found only on the plasma membrane of the B lymphocyte that synthesized the antibody, has distinct carboxy terminal sequences that include approximately 26 uncharged, hydrophobic side chains followed by variable numbers of charged (usually basic) amino acids that form the cytoplasmic segments (Fig. 3-5). This structural motif is characteristic of transmembrane proteins. The hydrophobic residues are believed to form an α-helix, which extends across the hydrophobic portion of the membrane lipid bilayer; the basic side chains of the cytoplasmic amino acids interact with the phospholipid head groups on the cytoplasmic surface of the membrane. In membrane IgM or IgD, the extreme carboxy terminus or cytoplasmic portion of the heavy chain is very short, only three amino acid residues; in membrane IgG or IgE, it is somewhat longer, up to about 30 amino acid residues in length.

The secretory forms of μ, α, and δ heavy chains, but not γ or ϵ, have additional extended nonglobular sequences on the carboxy-terminal side of the last C_H domain. These extensions are called **tail pieces.** In secreted IgM and IgA molecules, the tail pieces permit intermolecular interactions, resulting in multimeric Ig molecules. Specifically, IgM forms a pentamer, containing ten heavy chains and ten light chains, and IgA can form dimers containing four heavy chains and four light chains, or trimers, containing six heavy chains and six light chains (Fig. 3-6). Little is known about the usual form of circulating IgD because it is normally present in only trace amounts. Multimeric IgM and IgA also contain an additional 15 kD polypeptide, called the **joining (J) chain,** which is disulfide-bonded to the tail pieces, stabilizing the multimer. All membrane Ig molecules, regardless of isotype, are believed to be monomeric, containing two heavy and two light chains.

All heavy chains are characteristically N-glycosylated; that is, the polypeptide contains N-linked oligosaccharide groups attached to asparagine side chains. The location of oligosaccharides may vary in different Ig isotypes. The precise composition of the oligosaccharides is not fully determined by the polypeptide sequence and may also vary with the physiologic state of the host at the time of antibody synthesis.

ASSOCIATION OF LIGHT AND HEAVY CHAINS

The basic pattern of chain association in all antibody molecules is that each light chain is attached to a heavy chain and each heavy chain pairs with another heavy chain. The interactions between light and heavy chains involve both covalent and non-covalent interactions (see Fig. 3-2). Covalent interactions are in the form of disulfide bonds between the carboxy terminus of the light chain and the carboxy terminal region of the V_H domain or of the C_H1 domain of the heavy chain. The exact position of the heavy chain cysteine that participates in disulfide bond formation varies with the isotype. Non-covalent interactions arise primarily from hydrophobic interactions between the C_L domain and the C_H1 domain. This association of C_L and C_H1 brings the V_L and V_H domains into spatial apposition such that the juxtaposed V domains can each contribute to the binding of antigen (see Plate I, opposite page 52).

The pairing of heavy chains is best understood from studies of IgG molecules. As in the case of light and heavy chain association, both covalent and noncovalent interactions are involved. Heavy chains form interchain disulfide bonds in the region near the carboxy terminus of the hinge. Strong hydrophobic in-